REMARKS

Status of the Claims

Claims 36-40 are pending. Claims 36-40 are rejected.

Claim 36 is amended. No new matter is added to these claims.

Claim amendments

Claim 36 is amended to overcome the 35 U.S.C. §103 rejections. Amended claim 36 is drawn to a method of screening for a compound that inhibits virus binding and entry to target cell. This method comprises the steps of attaching an enzyme to the C-terminal end of a viral envelope protein, thereby creating an envelope-enzyme fusion protein. Virus particles comprising the fusion protein and wild type viral envelope protein are generated such that the enzyme in the envelope-enzyme fusion protein is incorporated into the virus particles. Target cells are then infected with these viral particles in the presence or absence of the compound and the activities of the enzyme in the infected cells are then measured. Decreased enzyme activities in the presence of the compound indicates that the compound inhibits virus binding and entry to the target cells mediated by the wild type envelope protein.

Double Patenting Rejection

Claim 36 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims

1, 8 and 9 if co-pending Application No. 11/036,568. Applicant respectfully traverses this rejection.

The Examiner states although the conflicting claims are not identical, they are not patentably distinct form each other because claims 1, 8 and 9 of Application No. 11/036,568 are drawn to screening for a compound that inhibits virus binding and entry into a target cell with a virus particle comprising an envelope-fusion protein and measuring the level of enzyme in infected cells. This concept is identical to the instant concept of claim 36.

Applicant will submit a terminal disclaimer to obviate this double patenting rejection.

The 35 U.S.C. §103 Rejection

Claims 36 and 39 are rejected under 35 U.S.C. §103(a) as being unpatentable over **Dulbeco** (US 4,593,002) or **Young** *et al* (US 5,916,563), either reference in further view of **Blumenthal** *et al* (J Biol Chem; 1987:262(28): 13614-13619). Applicant respectfully traverses this rejection.

The Examiner states that **Dulbeco** teaches viruses with wild-type and chimeric envelope/capsid proteins expressed on their surfaces where presence of the chimeric envelope proteins do not affect reproductive abilities of the viruses (col. 2, lines 50-54; col. 3, lines 54-68; col. 6, lines 35-44; col. 8, lines 13-17; col. 11, lines 40-50 and claims 1-7) and suggests incorporating proteins into the envelope fusion that have the enzymatic activity (col. 7, lines 51-59).

The Examiner further states that **Young** et al. teach a parvovirus with wild type VP2 capsid proteins and chimeric VP1 proteins fused with an enzyme (col. 2, lines 18-20; col. 5, lines 18-37; col. 7, line 58 to col. 8, line 52 and claims 1-3, 6 and 7). Although neither **Dulbeco** nor **Young** *et al* teach using the heterologous enzyme tag as a detection agent to screen compounds that inhibit virus binding, the Examiner states that **Blumenthal** *et al* teach vesicular stomatitis virus with enveloped proteins labeled with an octadecyl rhodamine (R18) fluorescent probe (pg 13614-13615). The amount of signal generated by the fluorescent probe on the virus was measured in the presence of competitor molecules molecules (unlabeled VSV, specific chemical inhibitors and neutralizing antibodies) and correlated with the quantity of labeled virus that attached to target cells (pg. 13616-second paragraph, page 13617; Figure1b; Table 1 and Figure 2).

Thus, the Examiner concludes that one of ordinary skill in the art at the time the invention was made either would have been motivated to use the heterologous enzyme fused to the envelope of **Dulbeco** or **Young** *et al*, as an indicator to measure virus-cell fusion in the presence of inhibitors, as evidenced by **Blumenthal** *et al* or would have had a reasonable expectation of success in using the heterologous enzyme of **Dulbeco** or **Young** *et al* to quantify virus-cell attachment in presence of candidate inhibitors because the heterologous enzyme of **Dulbeco** or **Young** *et al* does not interfere with viral propagation or native viral tropism (claims 2-4 (**Dulbeco**) or col. 5, lines 29-35 (**Young**)). Alternatively, the Examiner states that it would have been prima facie obvious to one of ordinary

skill in the art at the time the invention was made to fuse a detectable enzyme to an envelope protein as taught by **Dulbeco** or **Young** et al on the surface of VSV of **Blumenthal** *et al* with reasonable expectation of success since the fluorescent probe of **Blumenthal** *et al* is inserted into the viral bilayer (bridging pages 13614-13615).

Claim 36 is amended as discussed supra. The instant invention is drawn to rapid and high-throughput non-radioactive detection and quantitative assessment of virus entry. The assay described in the instant invention is unique in terms of modifying the virus. As taught in the instant invention, although the reporter enzyme was attached to the C-terminal of the virus envelope protein of murine leukemia virus, this reporter enzyme was incorporated into virus particles that were generated by transfection of cells with the wild type envelope protein, the fusion protein and plasmids encoding virus structural proteins. The reporter enzyme was then released into the cytoplasm of the virus particle after the construct was processed by viral protease. Since the viral membrane remained intact and the enzyme was inside the virus, the enzyme was shielded from its substrates. The entry of the virus partice into cell resulted in breaching of the the membrane and release of the enzyme whose activity could then be measured (page 4, line 10-page 5, line 3; page 11, lines 3-29; Example 1). In other words, the enzyme is encapsulated into the virus particle and released only when the membrane is breached.

In distinct contrast, although the cited prior art references teach of chimeric envelope/capsid proteins and using proteins that have enzymatic

activity or heterologous enzyme tags, these proteins or tags are attached externally. For instance, **Blumenthal** *et al* describe fluorescent labeling of the virus where the virus is labeled on the external surface (pg. 13614-13615). The cited prior art references neither teach nor suggest encapsulating the enzyme in the virus as taught by the instant invention. Thus, based on the combined teaching of the cited prior art references, it might have been obvious to one of ordinary skill in the art to label the virus externally with the enzyme and not motivate one to encapsulate the enzyme. Furthermore, since the virus taught by the cited prior art references is labeled externally with the enzyme, there is a greater possibility for the enzyme to be exposed to its substrates before entry of the virus or action of entry inhibitors. Therefore, although such a virus may provide information regarding virus binding, it may not be efficient in providing information regarding the viral entry mechanism or the action of entry inhibitors. Hence, the cited prior art references combined would not provide a person of ordinary skill in the art with reasonable expectation of success in using a virus that has been labeled externally to measure virus entry or action of entry inhibitors.

Applicant asserts that obviousness requires that the prior art relied upon fairly teach or suggest all the elements of the instant invention and that an incentive or motivation be present in the cited prior art references to produce the claimed invention with reasonable expectation of success in its production. Applicant has shown that the cited prior art references do not teach or suggest all claim limitations and that there is no motivation in the combination of the cited prior

art references to arrive at the instant invention with reasonable expectation of success. Therefore, Applicant contends that the instant invention is not prima facie obvious to one of ordinary skill in the art. Accordingly, based on the above-mentioned amendment and remarks, Applicant respectfully request the withdrawal of rejections of claims 36 and 39 are rejected under 35 U.S.C. §103(a).

Claims 36, 38 and 39 are rejected under 35 U.S.C. §103(a) as being unpatentable over **Russel** *et al.* (WO 94/06920) and **Blumenthal** et al supra. Applicant respectfully traverses this rejection.

The Examiner states that **Russel** *et al* teach a murine leukemia virus comprising an envelope fusion with a heterologous protein, such as functional enzyme (2nd para, page 11, the bridging pages 35-36,section 7 on page 38 and claims 1-4, 6 and 7). Additionally, the Examiner cites the same teachings of **Blumenthal** *et al* as discussed supra. Based on this, the Examiner states that one of ordinary skill in the art at the time the invention was made would have been motivated to use the heterologous enzyme fused to the envelope of **Russel** *et al* as an indicator to measure virus-cell fusion in the presence of inhibitors, as evidenced by **Blumenthal** *et al.* Furthermore, the Examiner states that one of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of using the heterologous enzyme of **Russel** *et al* to quantify virus-cell attachment in the presence of candidate inhibitors because the heterologous enzyme of **Russel** *et al* does not interfere with the viral propagation or native viral tropism (abstract, claims 4 and

7). Alternatively, the Examiner states that it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to fuse an enzyme to an envelope protein as taught by **Russel** *et al*, on surface of the VSV of **Blumenthal** *et al* with a reasonable expectation of success since the fluorescent probe of **Blumenthal** *et al* is inserted into the viral bilayer (bridging pages 13614-13615).

The instant invention and the instant claim 36 is as discussed by the Applicant supra. Although **Russel** *et al* and **Blumenthal** *et al* combined teach attaching a heterologous protein to the envelope protein of the virus (**Russel** *et al.*: claims 1-4, abstract, **Blumenthal** *et al.*: bridging pages 13614-13615), the attachment results in the heterologous protein being displayed on the outside and not incorporated in the virus as taught by the instant invention. The cited prior art references neither teach nor suggest encapsulating the enzyme. Thus, based on the combined teachings of the cited prior art references, it would be obvious to one of ordinary skill in the art to label the virus with the enzyme such that the enzyme is displayed externally and not motivate one to encapsulate the enzyme. Furthermore, since the virus taught by the cited prior art references combined is labeled externally with the enzyme, there is a greater possibility for the enzyme to be exposed to its substrates before entry of the virus or action of entry inhibitors. Therefore, although such a virus may provide information regarding virus binding, it may not be efficient in providing information regarding the viral entry mechanism or the action of entry inhibitors. Hence, the cited prior art references combined would not provide one of ordinary skill in the art with

reasonable expectation of success in using a virus that has been labeled externally to measure virus entry or action of entry inhibitors.

Applicant asserts that obviousness requires that the prior art relied upon fairly teach or suggest all the elements of the instant invention and that an incentive or motivation be present in the prior art to produce the claimed invention with reasonable expectation of success in its production. Applicant has shown that the cited prior art references do not teach or suggest all claim limitations and that there is no motivation in the combination of cited prior art references to arrive at the instant invention with a reasonable expectation of success. Therefore, Applicant contends that the instant invention is not prima facie obvious to one of ordinary skill in the art. Accordingly, based on above-mentioned amendment and remarks, Applicant respectfully requests the withdrawal of rejections of claims 36, 38 and 39 are rejected under 35 U.S.C. §103(a).

Claims 37 and 40 are rejected under 35 U.S.C. §103(a) as being unpatentable over **Dulbeco** or **Young** *et al.*, either in view of **Blumenthal** *et al* as applied to claims 36 and 39 or **Russel** *et al* and **Blumenthal** *et al* as applied to claims 36, 38 and 39 above and further in view of **Goldsmith** *et al* (US 6,451,598 B1). Applicant respectfully traverses this rejection.

The Examiner states that while **Russel** *et al* teach detection of the fusion protein in 96-well plates (page 46), none of the references cited teach using luciferase or measuring enzyme activity in 96-well plates. However, the

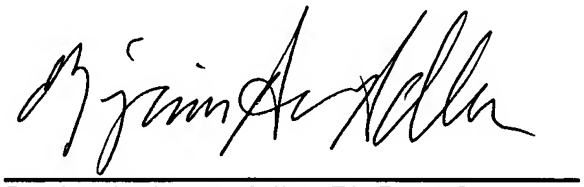
Examiner states that **Goldsmith** *et al* describe a cell fusion assay that uses luciferase as a reporter enzyme to indicate whether virus-cell fusion occurs in the presence of a candidate inhibitor (abstract, col. 2, line 13 to col. 5, line 29, col. 8, lines 1-42 and claims 1-16). In the cell fusion assay of **Goldsmith** *et al.*, the first cell is analogous to the virus expressing native and envelope-enzyme fusion proteins of **Dulbeco** or **Young** *et al* or **Russel** *et al.* Therefore, the use of luciferase to quantify virus cell fusions in the presence of candidate inhibitor compounds would have been obvious selection for use as fused detectable enzyme of **Dulbeco** or **Young** *et al* or **Russel** *et al* in view of **Blumenthal** *et al.* The Examiner further states that although none of the references teach assaying the enzymatic activity in 96-well plates, the ordinary artisan would have been motivated to use this type of plate in order to screen as many as 94 candidate inhibitors (and comparing the enzyme activities observed with positive and negative control samples) since conventional luminometers in the art accomodate this type of platform to quantify luciferase activity.

As discussed above, independent claim 36 is not obvious over the combined teachings of **Dulbeco**, **Young** *et al* and **Blumenthal** *et al* or **Russel** *et al* and **Blumenthal** *et al.* Therefore, claims 37 and 40 are not obvious over these cited prior art references either. Furthermore, the citation of **Goldsmith** *et al* does not render the independent claim 36 nor its dependent claims 37 and 40 obvious. Accordingly, based on the above-mentioned amendment and remarks, Applicant respectfully requests the withdrawal of rejection of claims 37 and 40 under 35 U.S.C. §103(a).

This is intended to be a complete response to the Office Action mailed November 07, 2005. Applicants submit that the pending claims are in condition for allowance. If any issues remain outstanding, please telephone the undersigned attorney of record for immediate resolution.

Respectfully submitted,

Date: April 7, 2006



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